

Pub. No. US 2006/0040894 A1, Hunter, et al.

HA and Lidocaine in the Prior Art

US 2006/0040894 A1

Feb. 23, 2006

21

boxymethyl cellulose all at 10 mg/ml. In order to attain this concentration a dose of approximately 10 times that required dose per ml may be needed (e.g., a total weight of 10 mg indometacin, 20 mg of sulphated polysaccharides, 100 mg of propylene glycol, TRITON, PEG, SPAN, PLURONIC or carboxymethyl cellulose) in an area or volume that may be exposed to a few ml of aqueous body fluid. So, for example, if 1 ml of an HA solution was injected where the injection fluid may be exposed to perhaps 2 ml of interstitial fluid diffusing past the area then a dose of 100 mg of each of these inhibitors would be recommended to ensure attainment of a dose of 10 mg per ml for some time after. The dosing needs depend largely of the injection *volume* and *area* of application. At sites with a higher hyaluronidase inhibitor may be given inhibitor was released in a controlled-metric dosage form then the application calculated by one skilled in the art based on profiles, site of application, turn over area and other parameters such as

[0177] 4. III-Loaded Hyaluronic

[0178] A variety of injectable hyaluronic acid products have been developed for soft tissue facial scars, diminish facial lines. Specifically, such implants are indicated for a variety of contour deficiencies including (i) correction of acne scars, atrophy glabellar frown lines, nasolabial fold, rhinoplasty, skin graft or other tissue defects. Manufactured synthetic hyaluronic acid commercially available for this purpose include PERLANE and HYLAFORM (B) from Genzyme Corporation. Other HA products that may be combined in cosmetic injections include: ACI Kaisha, Ltd. (Japan), JUVADERM from L.E.A. Derm (France), MACDERMOL from Laboratoires O.R. GE V. MacDermol (France), and ROFILAN Hylan Gel from Rofil Medical International (Holland).

[0179] Unfortunately, repeated "touch up" procedures are often required as the implant is colonized by host connective tissue cells and inflammatory cells which produce hyaluronidase and other enzymes capable of breaking down the HA implant over time. An injectable hyaluronic acid containing a hyaluronidase inhibitor (III), both alone or in a sustained release preparation, can result in increased durability of the implant and reduce the number of subsequent repeat injections. Although any of the previously described hyaluronidase inhibitors may be suitable for incorporation into a dermal HA injection, the following are particularly preferred: aurothiomalate, indometacin, propylene glycol, dextran sulphate, fucoidan, heparan, flavonoids, agents that modulate allergic reactions, phenolic compounds, and carboxymethyl cellulose.

[0180] Regardless of the formulation utilized, administration of the III-loaded HA injection may proceed in the following manner. A pre-loaded syringe with a fine gauge needle (30 or 32 gauge) containing the III-HA implant material is used. The patient is placed in a sitting position with the table back slightly reclined. Topical lidocaine and/or prilocaine can be used for anesthesia. The needle is inserted at an angle to the skin and advanced into the

superficial dermal tissue. A sufficient amount of implant material is extruded to repair the soft tissue contour defect. In the case of III-loaded RESTYLANE, overcorrection (injection of more material than is ultimately needed) is required as some of the injected material dissipates in the hours following injection. III-loaded PERLANE is typically used to correct deeper lines and is injected deeper into the dermis.

[0181] Representative examples of hyaluronic acid compositions used in cosmetic surgery injections are described in U.S. Pat. Nos. 5,633,001; 5,256,140; and 6,703,041.

[0183] The HA-HI composition may further comprise an anesthetic such as lidocaine, benzocaine or prilocalne and/or a neurotoxin such as a botulinum toxin.

REPEL or FLOWGEL, and other low molecular weight polymers that can be excreted.

[0183] The HA-HI composition may further comprise an anesthetic such as lidocaine, benzocaine or prilocalne and/or a neurotoxin such as a botulinum toxin.

[0184] It should be apparent to one of skill in the art that potentially any hyaluronidase inhibitor may be utilized alone, or in combination, in the practice of this embodiment as described above. Exemplary III agents for use in combination with HA in cosmetic injection procedures include aurothiomalate, indometacin, propylene glycol, carboxymethyl cellulose, dextran sulphate, fucoidan and heparin, as well as analogues and derivatives of the aforementioned.

[0185] Suitable doses of these compounds may be such as to provide a steady concentration of each agent to elicit a prolonged inhibitory effect on hyaluronidase. These concentrations are approximate and may be adjusted depending on the potency of the compound and duration of effect required: aurothiomalate 10 mM, indometacin 1 mg/ml, heparin 1 mg/ml, sulphated polysaccharides 2 mg/ml, and propylene glycol, TRITON X-100, PEG, SPAN, PLURONIC L101, and carboxymethyl cellulose all at 10 mg/ml. In order to attain this concentration a dose of approximately 10 times that required dose per ml may be needed (e.g., a total weight of 10 mg indometacin, 20 mg of sulphated polysaccharides, 100 mg of propylene glycol, TRITON, PEG, SPAN, PLURONIC or carboxymethyl cellulose) in an area that may be

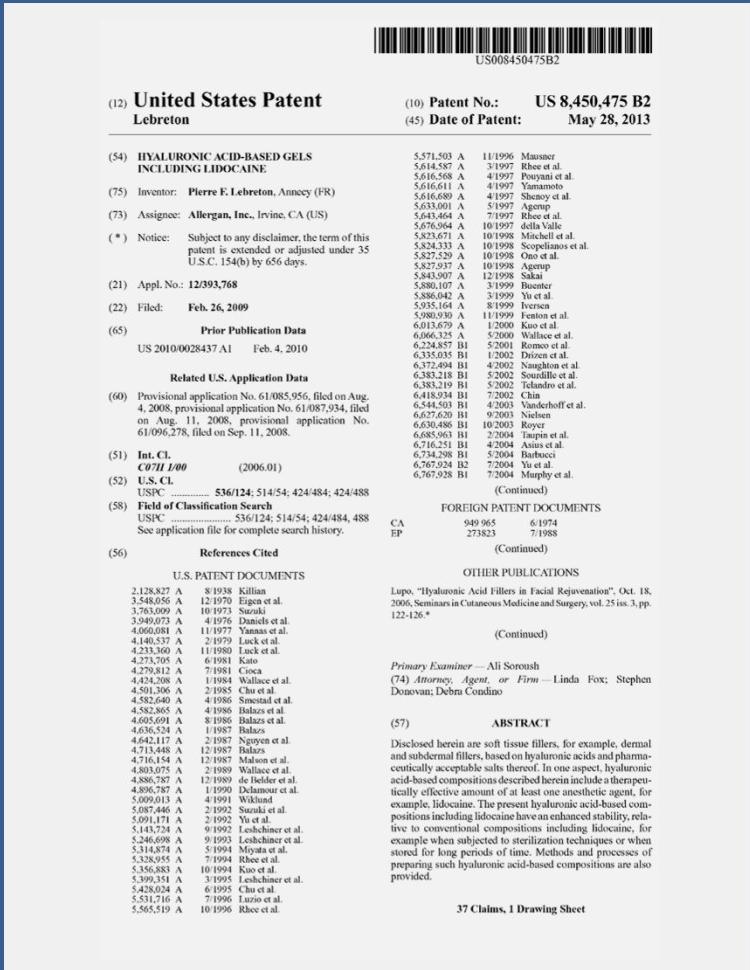
Lidocaine in the Prior Art

Crosslinked HA Fillers with Lidocaine Were Already Used

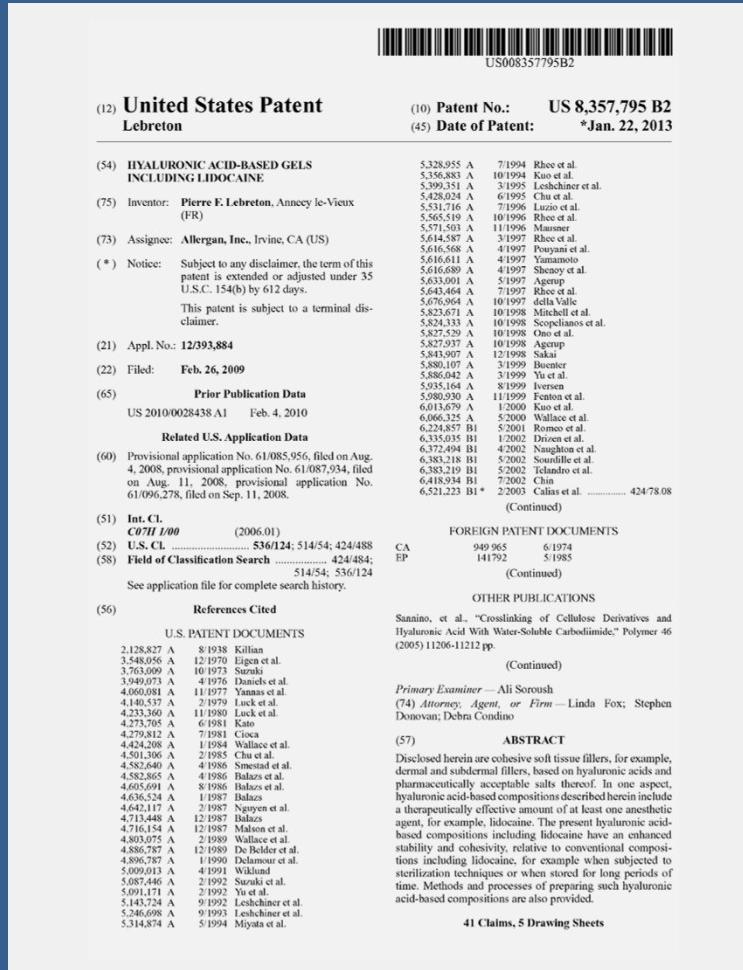


Patents In Dispute

US Patent No. 8,450,475 B2



US Patent No. 8,357,795 B2



Law of Claim Construction

Claim construction favors the meaning that “most naturally aligns with the patent's description of the invention.”

Phillips v. AWH Corp., 415 F.3d 1316 (Fed. Cir. 2005)(en banc)

"[T]he focus in claim construction is on 'the meaning of claim terms within the patent,' and not on the abstract meaning of words."

*Reflex Packaging Inc. v. Lenovo (United States), Inc., No. 5:10-CV-01002-EJD, 2012 U.S. Dist. LEXIS 64594, at *20 (N.D. Cal. May 8, 2012)*

First Disputed Term: “Stable”

Claim Term (Claim)	Plaintiffs' Construction	Defendants' Construction
Stable (1, 18, 27, 31, 34)	Resists chemical and physical decomposition	Maintains one of the following aspects: transparent appearance, pH, extrusion force and/or rheological characteristics, hyaluronic acid (HA) concentration, sterility, osmolarity, and lidocaine concentration

'475 Patent, Lebreton

Definition of Stable

US 8,450,475 B2

3

In still another embodiment, the soft tissue filler composition has an extrusion force of between about 10 N and about 13 N, for example, at a rate of about 12.5 mm/minute. In yet another embodiment, the composition has a viscosity of between about 5 Pa·s and about 450 Pa·s, for example, when measured at about 5 Hz.

In one embodiment, the HA component is a gel, for example, a cohesive, hydrated gel. In one embodiment, the HA component is a crosslinked HA gel having no greater than about 1% to about 10% free HA. For purposes of this disclosure, free HA includes truly uncrosslinked HA as well as lightly crosslinked HA chains and fragments, all in soluble form in water.

In yet other embodiments, the HA component comprises greater than about 10%, for example, greater than about 15%, for example, up to or greater than about 20% free HA.

In yet another embodiment, the HA component is a gel comprising particles of crosslinked HA in a relatively fluid medium of free HA. In some embodiments, the HA component has an average particle size of greater than about 200 µm, for example, greater than about 250 µm.

Further described herein is a soft tissue filler composition comprising a HA component crosslinked with 1,4-butanediol diglycidyl ether (BDDDE), said HA component having a degree of crosslinking of less than about 5%, for example, about 2%, and an anesthetic component having a concentration between about 0.1% and about 5.0% by weight of the soft tissue filler composition, wherein the anesthetic is lidocaine.

Further described herein are methods of preparing soft tissue filler compositions, the methods comprising the steps of: providing a HA component crosslinked with at least one crosslinking agent selected from the group consisting of 1,4-butanediol diglycidyl ether (BDDDE), 1,4-bis(2,3-epoxypropoxy)butane, 1,4-bisglycidylbutyrate, 1,2-bis(2,3-epoxypropoxy)ethylene and 1-(2,3-epoxypropyl)-2,3-epoxycyclohexane, and 1,4-butanediol diglycidyl ether or combinations thereof; adjusting the pH of said HA component to an adjusted pH above about 7.2; and adding a solution containing at least one anesthetic agent to the HA component having the adjusted pH to obtain a HA-based filler composition.

In another embodiment, the composition is sterilized, for example, by autoclaving, to form a sterilized composition and wherein the sterilized composition is stable of ambient temperature for at least about 6 months, for example, at least 9 months, at least about 12 months or more.

In still another embodiment, the adjusted pH is above about 7.5. In another embodiment, the method further comprises the step of homogenizing the HA component during or after the step of adding the solution containing the at least one anesthetic agent. In a further embodiment, the step of homogenizing comprises subjecting the composition to mixing with a controlled shear.

In another embodiment, the step of providing a HA component comprises providing dry free NaHA material and hydrating the dry free NaHA material in an alkaline solution to obtain an alkaline, free NaHA gel. In yet another embodiment, the alkaline, free NaHA gel has a pH greater than about 8.0. In still another embodiment the pH is greater than about 10.

In a further embodiment, the HA component comprises greater than about 20% free HA and the crosslinked portion of the HA component has a degree of crosslinking of less than about 6% or less than about 5%.

In still a further embodiment, the soft tissue filler composition has a particulate nature in that it comprises particles of crosslinked HA dispersed in a fluid soluble HA medium. In

some embodiments, the average size of such particles is at least about 200 µm, and in other embodiments the average size of such particles is at least about 250 µm.

10
15
20
25
30
35
40
45
50
55
60
65

co
wi
pa
an
al
co
pr
th
m
al
er
er
er
ad
fil
po
co
fil
fil
ha
a
re
th
m
m
fo
(I
cc
de
di
on
Fo
co
M
ha
m
M
w
ab
M
m
ex
di
65

Some definitions are provided below:

DEFINITIONS

Certain terms as used in the specification are intended to refer to the following definitions, as detailed below. Where the definition of terms departs from the commonly used meaning of the term, applicant intends to utilize the definitions provided below, unless specifically indicated.

Autoclave stable or stable to autoclaving as used herein describes a product or composition that is resistant to degradation such that the product or composition maintains at least one, and preferably all, of the following aspects after effective autoclave sterilization: transparent appearance, pH, extrusion force and/or rheological characteristics, hyaluronic acid (HA) concentration, sterility, osmolarity, and lidocaine concentration.

Patentee Can Be His Own Lexicographer

Where the "patent expresses an intention to impart a novel meaning to claim terms,"¹ that definition "controls the meaning of [the claim term], regardless of any potential conflict with the term's ordinary meaning"² Thus, a claim term should not be given its "plain and ordinary meaning" where "the patentee demonstrated an intent to deviate from the ordinary and accustomed meaning of a claim term by redefining the term"³ These changes to a term's definition can be found not only in the patent itself, but also the prosecution history, which can "provide[] evidence of how the PTO and the inventor understood the patent."⁴

¹*SunRace Roots Enter. Co. v. SRAM Corp.*, 336 F.3d 1298, 1302 (Fed. Cir. 2003).

²*3M Innovative Props. Co. v. Avery Dennison Corp.*, 350 F.3d 1365, 1374 (Fed. Cir. 2003).

³*SunRace*, 336 F.3d at 1304.

⁴*Phillips*, 415 F.3d at 1317; *Vitronics*, 90 F.3d at 1582-83.

'475 Patent, Lebreton

Definition of Stable

US 8,450,475 B2

5

ing agent to HA-monomeric units within the crosslinked portion of the HA-based composition. It is measured by the weight ratio of HA monomers to crosslinker (HA monomers: crosslinker).

Free HA as used herein refers to individual HA polymer molecules that are not crosslinked to, or very lightly crosslinked to (very low degree of crosslinking) the highly crosslinked (higher degree of crosslinking) macromolecular structure making up the soft tissue filler composition. Free HA generally remains water soluble. Free HA can alternatively be defined as the "uncrosslinked," or lightly crosslinked component of the macromolecular structure making up the soft tissue filler composition disclosed herein.

Cohesive as used herein refers to the ability of a HA-based composition to retain its shape and resist deformation. Cohesiveness is affected by, among other factors, the initial HA:crosslinker ratio of the initial free HA followed by, among other factors, the pH of the HA-based composition pH. A cohesive composition resists phase separation when tested according to Example I herein.

DETAILED DESCRIPTION

The present disclosure generally relates, for example, dermal and subdermal hyaluronic acids (HA) and pharmaceutical compositions containing HA, for example, sodium hyaluronate. HA-based compositions disclosed herein include therapeutically effective amounts of lidocaine. The compositions, including at least one active agent, provide enhanced stability, relative to conventional compositions including, for example, to high temperatures and pressures experienced during heat and/or pressure processing, for example, autoclaving, and/or for ambient temperature for an extended period of time.

The stable compositions maintain the following aspects after effect and/or prolonged storage: transparency in a patient, extrusion force and/or rheological properties, HA concentration, sterility, concentration. Methods or processes for preparing HA-based compositions are also provided by such methods or processes.

As used herein, hyaluronic acid includes hyaluronic acid salts, and includes, but is not limited to, sodium hyaluronate (NaHA), potassium hyaluronate, calcium hyaluronate.

Generally, the concentration of HA described herein is preferably at least 10 mg/mL and up to about 40 mg/mL. For example, the concentration of HA in some of the compositions is in a range between about 20 mg/mL and about 30 mg/mL. Further, for example, in some embodiments, the compositions have a HA concentration of about 22 mg/mL, about 24 mg/mL, about 26 mg/mL, or about 28 mg/mL.

In addition, the concentration of one or more anesthetics is in an amount effective to mitigate pain experienced upon injection of the composition. The at least one local anesthetic can be selected from the group of ambacaine, amilonane, amylcaine, benoxinate, benzocaine, betoxycaine, biphennamine, bupivacaine, butacaine, butabutin, butaflincaine, butethamine, butoxycaine, carficaaine, chloroprocaine, cocaine, cocaethylene, cocaine, cyclomethycaine, dibucaine, dimethisoquin, dimethocaine, diperodon, dicyclomine, egonidine,

6

egonidine, ethyl chloride, etidocaine, beta-egonidine, euprocain, fenacaine, fomacaine, hexylcaine, hydroxytetracaine, isobutyl p-aminobenzoate, leucocaine mesylate, levocetadrol, lidocaine, mepivacaine, meprylcaine, metabutoxycaine, methyl chloride, myrtacaine, naphaine, octocaine, orthocaine, oxethazaine, parethoxycaine, phenacaine, phenol, piperocaine, piridocaine, polidocanol, pramoxine, prilocaine, procaine, propanocaine, proparacaine, propipocaine, propoxyceaine, pseudococaine, pyroccaine, ropivacaine, salicyl alcohol, tetracaine, tolycaine, trimecaine, zolamine, and salts thereof. In one embodiment, the at least one anesthetic agent is lidocaine, such as in the form of lidocaine HCl. The compositions described herein may have a lidocaine concentration of between about 0.1% and about 5% by weight (about 0.2% to about 0.7% by weight).

The stable compositions maintain at least one of, or all of, the following aspects after effective autoclave sterilization and/or prolonged storage: transparent appearance, pH for use in a patient, extrusion force and/or rheological characteristics, HA concentration, sterility, osmolarity, and lidocaine concentration.

appearance and other characteristics, such as color, which are maintained for a lengthy period of time, for example, for a period of time of at least 6 months to a year or more, and even after being subjected to sterilization procedures, for example, autoclaving.

It is a surprising discovery that formulations of crosslinked HA-based compositions including lidocaine can be manufactured in a manner in accordance with the invention to produce sterilization-stable, injectable HA/lidocaine compositions.

Further described herein is a method for preparing stable

HA-based compositions containing an effective amount of lidocaine by preparing a cohesive, crosslinked HA-based precursor composition, adding lidocaine chloride to the precursor composition to form a HA/lidocaine gel mixture, and homogenizing the mixture, to obtain a crosslinked HA-based composition that is stable to autoclaving.

In certain embodiments, the precursor composition is a gel which includes less than about 1% of soluble-liquid form or

'475 Patent, Lebreton

Definition of Stable

US 8,450,475 B2

13

between about 7.5 and about 8). The lidocaine HCl solution is then added to the slightly basic gel to reach a final desired concentration, for example, a concentration of about 0.3% (w/w). The resulting pH of the HA/lidocaine mixture is then about 7 and the HA concentration is about 24 mg/mL. Mechanical mixing is performed in order to obtain a proper homogeneity in a standard reactor equipped with an appropriate blender mechanism.

If desired, a suitable amount of free HA gel may be added to the HA/lidocaine gel mixture with the advantage of increasing the kinetics of lidocaine delivery. For example, free HA fibers are swollen in a phosphate buffer solution, in order to obtain a homogeneous viscoelastic gel. This free HA gel is then added to the crosslinked HA/lidocaine gel (for example, at about 5%, w/w). The resulting gel is then filled into Ready-to-Fill sterile syringes and autoclaved at sufficient temperatures and pressures for sterilization for at least about 1 minutes.

After autoclaving, the final HA/lidocaine product is packaged and distributed to physicians. The product manufactured in accordance with this method exhibits one or more characteristics of stability as defined elsewhere herein. For example, the autoclaved HA/lidocaine product has a viscosity, cohesivity, and extrusion force that are acceptable. No degradation of the HA/lidocaine gel product is found during testing of the product after the product has spent several months in storage.

Example 3

Properties of Soft Tissue Fillers

Table 2 provides a summary of stability testing results on the composition manufactured as described herein.

TABLE 2

Test	HA/lidocaine Composition		
	3 month results	6 month results	9 month results
Aspect Transparent and homogeneous	Conforms	Conforms	Conforms
pH	7.2	7.2	7.2
Extrusion Force (N)	11.9	11.1	11.9
NaHA Concentration (mg/g)	23.8	23.1	24.2
Sterility	Conforms	Conforms	Conforms
Osmolarity (mOsm/kg)	349	329	342
Lidocaine Content (%)	0.29	0.29	0.29
2,6-dimethylaniline content	Conforms	Conforms	Conforms

It was discovered that at 9 months time (from manufacture date), the composition continues to meet the product specifications.

Example 4

Kinetic Release

The following example illustrates the kinetic of release of lidocaine from cohesive HA gels according to the present description. The aim of the Example is to show that the lidocaine contained in HA gels according to the present description is freely released from the gels when placed in the skin.

Dialysis was performed for different periods of time (about 10 g of gel were placed in a small dialysis bag and then put in 30 g of water). After each dialysis was stopped at a given time, the gel was homogenized with a spatula and the amount of lidocaine was determined by UV method. The final concentration of the dialysis bath met the theoretical concentration of lidocaine which indicates the free release of lidocaine from the gel.

Table 3 illustrates lidocaine concentration in % (w/w), correction of the value and determination of the % of released lidocaine. Additionally, FIG. 1 graphically illustrates the results tabulated in Table 3 below. Within FIG. 1 is indicated the theoretical equilibrium concentration of lidocaine that would exist if the lidocaine were retained in the gel or if it were to be freely released. As is graphically illustrated therein, the data suggest that the lidocaine is freely released from the gel.

TABLE 3

	MMA4031- EC6	MMA4031- EC2	MMA4031- EC3	MMA4031- EC4	MMA4031- EC5	MMA4031- EC7
Dialysis time (h)	0 hr	1 hr 30 min	5 hr	7 hr	23 hr	48 hr
[lidocaine] (%)	0.29	0.20	0.16	0.15	0.08	0.07

Table 2 provides a summary of stability testing results on the composition manufactured as described herein.

TABLE 2

Test	HA/lidocaine Composition		
	3 month results	6 month results	9 month results
Aspect Transparent and homogeneous	Conforms	Conforms	Conforms
pH	7.2	7.2	7.2
Extrusion Force (N)	11.9	11.1	11.9
NaHA Concentration (mg/g)	23.8	23.1	24.2
Sterility	Conforms	Conforms	Conforms
Osmolarity (mOsm/kg)	349	329	342
Lidocaine Content (%)	0.29	0.29	0.29
2,6-dimethylaniline content	Conforms	Conforms	Conforms

It was discovered that at 9 months time (from manufacture date), the composition continues to meet the product specifications.

Second Disputed Term: “Crosslinked”

‘475 Patent

Claim Term (Claim)	Plaintiffs' Construction	Defendants' Construction
HA crosslinked with 1,4-butanediol diglycidyl ether (BDDE) / hyaluronic acid (HA) component crosslinked with 1,4-butanediol diglycidyl ether (BDDE) / (BDDE)-crosslinked hyaluronic acid (1, 18, 27, 31, 34)	HA that forms a macromolecular structure resulting from chemical linking of HA by BDDE	HA that has been covalently modified with BDDE to form a macromolecular structure that is water-insoluble , such that the degree of crosslinking is at least about 2% and is up to about 20% “Degree of crosslinking” as used herein has the same construction as agreed by the parties

Second Disputed Term: “Crosslinked”

‘795 Patent

Claim Term (Claim)	Plaintiffs' Construction	Defendants' Construction
Hyaluronic acid (HA) component crosslinked with a crosslinking agent (1)	HA that forms a macromolecular structure resulting from chemical linking of HA by a crosslinking agent	HA that has been covalently modified with a crosslinking agent to form a macromolecular structure that is water-insoluble , such that the degree of crosslinking is at least about 2% and is up to about 20% “Degree of crosslinking” as used herein has the same construction as agreed by the parties within the ‘475 Patent

Agreed-Upon Constructors

'475 Patent

Claim Term (Claim)	Agreed-Upon Construction
Degree of crosslinking (5-7, 18, 27, 31, 37)	<p>The percent weight ratio of crosslinking agent to HA monomeric units (HA disaccharide units) within the crosslinked portion of the HA based composition (i.e., (total mass of crosslinking agent / total mass of monomeric units) * 100))</p> <p>The “crosslinked portion of the HA based composition” as used herein has the same construction as the other terms referring to “crosslinked HA,” as construed by the court</p>

Second Disputed Term: “Crosslinked”

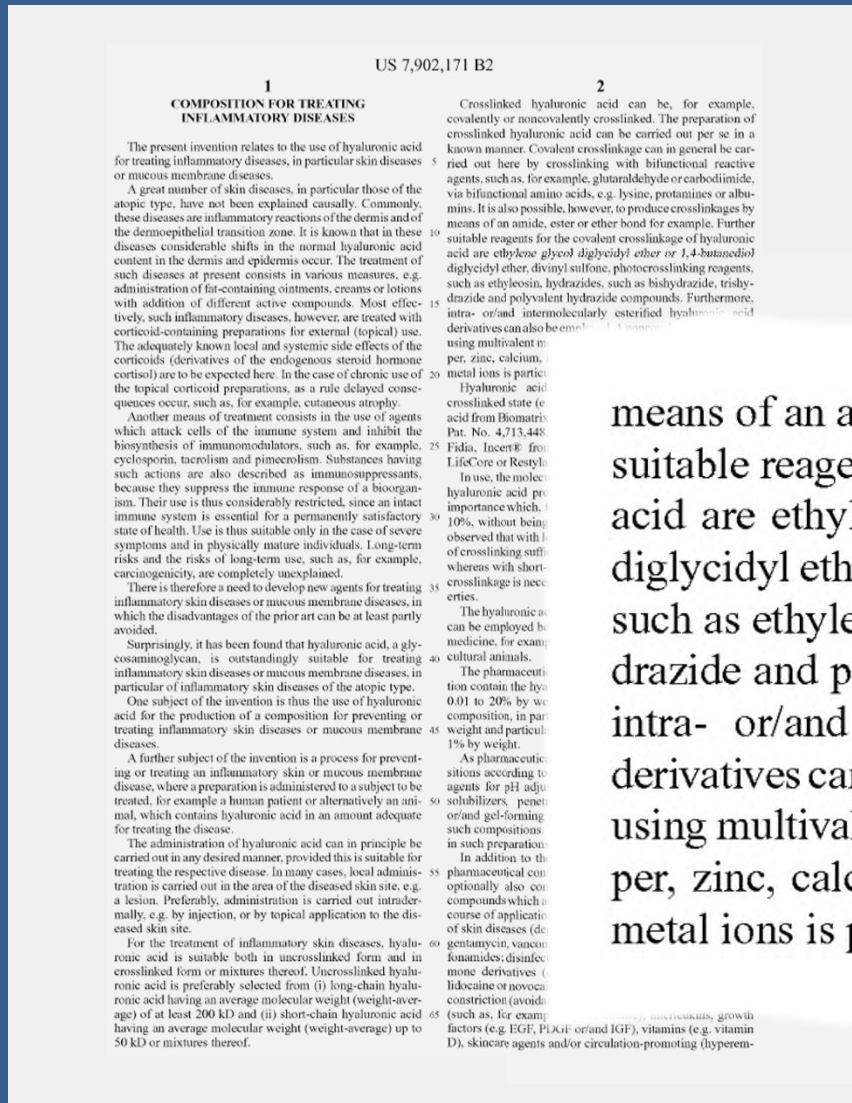
- Covalently modified
- Water-insoluble
- Degree of crosslinking

Second Disputed Term: “Crosslinked”

- Covalently modified
- Water-insoluble
- Degree of crosslinking

7,902,171 B2 Patent, Reinmuller

Art Describes Crosslinks as Covalent Bonds



Source: '171, 2:9-20